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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	10/028,224	BENSON ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-78* is/are pending in the application.

4a) Of the above claim(s) *1-53,77 and 78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

[1] Claims 1-78 are pending in the application.

[2] Applicant's amendment to the specification in Paper No. 13, filed June 11, 2003, is acknowledged.

[3] Receipt of six sheets of formal drawings in Paper No. 14 is acknowledged. The drawings have been reviewed and are accepted by the Draftsperson.

[4] Receipt of Information Disclosure Statements filed as Paper Nos. 8 and 11 is acknowledged. The information disclosure statements fail to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The examiner has made an earnest attempt to locate the missing references without success. The information disclosure statements have been placed in the application file, but the information referred to therein has not been considered.

Election/Restriction

[5] Applicant's election with traverse of Group IX, claims 72-76, drawn to a crystal of beta secretase, in Paper No. 13 is acknowledged. Applicant traverses the restriction by arguing Group VIII, claims 54-71, drawn to a method for crystallizing a human beta secretase molecule or molecular complex, and Group X, claims 77 and 78, drawn to a method for producing human beta secretase, can be co-examined without a serious burden on the examiner. To the extent applicant's argument applies to rejoinder of the claims of Group VIII with the elected claims of Group IX, applicant's argument is found persuasive and the claims of Group VIII will be co-examined with the claims of elected Group IX. However, applicant's argument regarding rejoinder of the claims of Group X with the claims of Group IX is not found persuasive. MPEP 808.02(c) states that a different field of search exists "[w]here it is necessary to search for one of the distinct subjects in places where no pertinent art to the other subject exists, a different field of search is shown". Groups IX and X are drawn to entirely different inventions and a search of each group would

require independent considerations which would require the examiner to focus on different features and entail differently structured text searches for both patent and non-patent literature for the claims of each of Groups IX and X. In the instant case, it is false to assume that disclosures teaching a method of producing a polypeptide would also disclose a crystal of the same polypeptide and vice versa. For example, Bruinzeel et al. (*Prot Exp Pur* 26:139-148) teach a method of producing human beta secretase without also disclosing a crystal of the protein produced thereby. Also, Ghosh et al. (*J Med Chem* 44:2865-2868) teach a crystal of human beta secretase without disclosing a method for producing the protein used for crystallization. As such, a different field of search is required for each of Groups IX and X and thus a serious burden is required for co-examination of the claims of elected Group IX and the claims of Group X.

[6] The requirement is still deemed proper and is therefore made FINAL.

[7] It is noted that a species election was required for the invention of Group VIII. In the event of rejoinder of Group VIII with Group IX, applicant elects the species of Groups J, K, and P with traverse. Applicant traverses the species election on the grounds that the generic claim includes sufficiently few species that a search and examination of all species would not impose a serious burden on the examiner. Upon reconsideration of the species election, the examiner hereby withdraws the species election and all claims of Group VIII will be co-examined with the claims of elected Group IX. Thus, applicant's argument traversing the species election requirement for Group VIII is rendered moot.

[8] Claims 1-53, 77, and 78 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

[9] Claims 54-76 are being examined on the merits.

Priority

[10] Applicant's claim for domestic priority to Application numbers 09/747,421, filed December 23, 2000 and 09/808,310, filed March 13, 2001 under 35 USC 120 is acknowledged. It is noted that the crystal of human beta secretase as disclosed in Application number 09/747,421 has a space group

symmetry of $P32_21$ (see, e.g., pages 3, 4, and 43 of the specification of Application number 09/747,421). The crystals of human beta secretases isolated from CHO and HEK 293 cells as disclosed in Application number 09/808,310 and the instant application have a space group symmetry of $P3_221$ (see, e.g., page 47 of the specification) and the crystal of human beta secretase isolated from insect cells as disclosed in Application number 09/808,310 and the instant application has a space group symmetry of $P32_21$ (see, e.g., pages 49 and 50 of the specifications).

Sequence Compliance

[11] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). In order to comply with the sequence requirement(s), applicant is required to identify nucleotide and/or amino acid sequences disclosed in the specification by a sequence identifier(see page 42, line 7 of the specification). If the sequence(s) are not already present in the computer readable form (CRF) and paper copy thereof, applicant is required to submit a computer readable form (CRF) of the "Sequence Listing" and a paper copy thereof, as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d).

Specification/Informalities

[12] The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification (page 26, line 14 and page 47, line 22) is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-

executable code is considered to be an improper incorporation by reference. See MPEP 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference.

[13] The specification is objected to as referring to a figure that is not present in the instant application. The specification discloses "Figure 1B" at page 45, line 24. However, there is no Figure 1B in the Figures or a description thereof in the "Brief Description of the Figures" at pages 11-12.

[14] The specification is objected to as being confusing in the disclosure of an invalid space group symmetry for crystals of human beta secretase isolated from insect cells. The specification discloses that crystals of human beta secretase isolated from insect cells having a space group symmetry of $P32_21$ (page 49, line 19). The space group $P32_21$ is an invalid space group. It appears this may be an editing error as this crystal is disclosed as having unit cell dimensions of a trigonal space group (see page 49, line 19 to page 50, line 1). For purposes of examination and in the interest of advancing prosecution, the examiner has interpreted the space group "$P32_21$" as disclosed in the specification as being "$P3_221$".

Claim Objections

[15] Claims 55 and 58 are objected to as using the improper alternative limitation "selected from the group of". While there is no uncertainty or ambiguity with respect to the question of scope or clarity of the claims, it is suggested that applicant use a proper alternative limitation by inserting the term "consisting" after "group" in line 1 of claims 55 and 58. See MPEP § 2173.05(h) regarding alternative limitations

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[16] Claims 55, 58, 71, and 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[17] Claim 55 recites the limitation "the salt". There is insufficient antecedent basis for this limitation in the claim. In accordance with MPEP § 2173.05(e), it is suggested that, for example, applicant amend claim 55 to depend from claim 59.

[18] Claim 58 recites the limitation "the glycol". There is insufficient antecedent basis for this limitation in the claim. In accordance with MPEP § 2173.05(e), it is suggested that, for example, claim 58 be amended to insert the term "wherein the solution comprises a glycol" following "The method of claim 54".

[19] Claim 71 recites the limitation "the Baculovirus expression system". There is insufficient antecedent basis for this limitation in the claim. In accordance with MPEP § 2173.05(e), it is suggested that, for example, applicant replace "the" in the term "the Baculovirus expression system" with "a".

[20] Claim 76 is confusing in that it is unclear as to how a crystallized polypeptide can have the amino acid sequence of SEQ ID NO:1 and *simultaneously* have a different amino acid sequence, i.e., SEQ ID NO:1 with at least one methionine replaced with selenomethionine. It is suggested that, for example, applicant amend claim 76 to depend from claim 74 instead of claim 75.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[21] Claims 54-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 54-71 are drawn to a method for crystallizing a genus of human beta secretase molecules or molecular complexes by preparing a genus of purified human beta secretases in the presence of a genus of inhibitors. Claims 72-76 are drawn to a genus of crystals of beta secretases from any source or the beta secretase of SEQ ID NO:1 optionally having methionine replaced with selenomethionine having the space group symmetry and/or unit cell dimensions as recited in the claims.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of purified human beta secretases, inhibitors thereof, or crystals of beta secretases from any source, i.e., a crystal of purified human beta secretase of SEQ ID NO:1 having a trigonal space group symmetry of $P3_221$ and the unit cell dimensions of a=b=112±20, c=110±20, and $\alpha=\beta=90^{\circ}$ and $\gamma=120^{\circ}$ or a=b=99±35, c=117±35, and $\alpha=\beta=90^{\circ}$ and $\gamma=120^{\circ}$ produced using purified human beta secretase of SEQ ID NO:1 in the presence of the inhibitor of Figure 1. The specification fails to describe any additional representative species of the claimed genera of purified human beta secretases, inhibitors thereof, or crystals of beta secretases from any source. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it also acknowledges

that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". The prior art discloses at least one homolog and several splice variants of human beta secretase (see for example, Farzan et al. *Proc Natl Acad Sci, USA* 97:9712-9717 and Ehehalt et al. *Biochem Biophys Res Commun* 293:30-37) with amino acid sequences that are distinct from the human beta secretase of SEQ ID NO:1. Furthermore, a trigonal space group requires a=b in the unit cell dimensions and, as written, the unit cell dimensions of a and b as recited in claims 73 and 74 are not required to be equivalent. Also, it is well known in the art that a hexagonal crystal system also has the unit cell dimensions of $\alpha=\beta=90^{\circ}$ and $\gamma=120^{\circ}$. Thus, the claimed genera of purified human beta secretases, inhibitors thereof, or crystals of beta secretases from any source encompasses species that are widely variant in amino acid sequence (beta secretases and human beta secretases), chemical structure (inhibitors of human beta secretases), and crystal structure including (but not limited to) homologs and allelic variants of human beta secretase or beta secretases from any source, *all* inhibitors of human beta secretase including beta secretases and inhibitors thereof yet to be isolated or discovered, and crystals of beta secretase having a trigonal and hexagonal crystal lattice with unit cell dimensions broadly ranging from a=about 77Å to about 147Å, b=77Å to about 147Å, and c=77Å to about 147Å. As such, the disclosure of the single representative species of a crystal of purified human beta secretase of SEQ ID NO:1 having a trigonal space group symmetry of $P3_221$ and the unit cell dimensions of a=b=112±20, c=110±20, and $\alpha=\beta=90^{\circ}$ and $\gamma=120^{\circ}$ or a=b=99±35, c=117±35, and $\alpha=\beta=90^{\circ}$ and $\gamma=120^{\circ}$ produced using purified human beta secretase of SEQ ID NO:1 in the presence of the inhibitor of Figure 1 is insufficient to be representative of the attributes and features of *all* species encompassed by the genera of purified human beta secretases, inhibitors thereof, or crystals of beta secretases from any source. Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[22] Claims 54-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for crystallizing the human beta secretase of SEQ ID NO:1 complexed with the human beta secretase inhibitor of Figure 1 by preparing purified human beta secretase of SEQ ID NO:1 in the presence of the inhibitor of Figure 1 to a final concentration of 18-40 mg/mL beta secretase protein and 2 mM inhibitor and crystallizing human beta secretase using the hanging drop method in a solution of 17-20% PEG 3000, 0.1 M sodium acetate, pH 4.5 at 20 degrees Celsius and optionally wherein the solution contains 10% glycerol or 10% ethylene glycol and a crystal of the human beta secretase of SEQ ID NO:1 having a trigonal space group symmetry of $P3_221$ and the unit cell dimensions of a=b=112±20, c=110±20, and $\alpha=\beta=90^\circ$ and $\gamma=120^\circ$ or a=b=99±35, c=117±35, and $\alpha=\beta=90^\circ$ and $\gamma=120^\circ$, does not reasonably provide enablement for a method for crystallizing *any* human beta secretase molecule or molecular complex by preparing purified human beta secretase in the presence of *any* inhibitor and crystallizing human beta secretase from *any* solution having a pH of about 3.5-5.5 and optionally under the conditions as recited in claims 55-71 or *all* crystals of beta secretase from any source having the trigonal space group symmetry $P3_221$ and/or the unit cell dimensions as recited in claim 73, and optionally wherein the beta secretase is SEQ ID NO:1 with at least one methionine replaced with selenomethionine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass a method for crystallizing *any* human beta secretase molecule or molecular complex by preparing purified human beta secretase in the presence of *any* inhibitor and crystallizing human beta secretase from *any* solution having a pH of about 3.5-5.5 and optionally under the conditions as recited in claims 55-71 or *all* crystals of beta secretase from any source having the trigonal space group symmetry $P3_221$ and/or the unit cell dimensions as recited in claim 73, and optionally wherein the beta secretase is SEQ ID NO:1 with at least one methionine replaced with selenomethionine. The broad scope of claimed methods for crystallizing human beta secretase and crystals of beta secretase from any source is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of beta secretases from any source, human beta secretases, inhibitors of human beta secretases, crystallization conditions, and crystal structures broadly encompassed by the claims. In this case the disclosure is limited to a method for crystallizing the human beta secretase of SEQ ID NO:1 complexed with the human beta secretase inhibitor of Figure 1 by preparing purified human beta secretase of SEQ ID NO:1 in the presence of the inhibitor of Figure 1 to a final concentration of 18-40 mg/mL protein and 2 mM inhibitor and crystallizing human beta secretase using the hanging drop method in a solution of 17-20% PEG 3000, 0.1 M sodium acetate, pH 4.5 at 20 degrees Celsius and optionally wherein the solution contains 10% glycerol or 10% ethylene glycol and a crystal of the human beta secretase of SEQ ID NO:1 having a trigonal space group symmetry of $P3_221$ and the unit cell dimensions of a=b=112±20, c=110±20, and $\alpha=\beta=90^\circ$ and $\gamma=120^\circ$ or a=b=99±35, c=117±35, and $\alpha=\beta=90^\circ$ and $\gamma=120^\circ$.

- The lack of guidance and working examples: The specification provides the working examples of methods for crystallizing the human beta secretase of SEQ ID NO:1 recombinantly produced in CHO, HEK293, or insect cells by the methods disclosed at pages 45-47 of the specification to generate a crystal having a trigonal space group symmetry of $P3_221$ and the unit cell dimensions of a=b=112±20, c=110±20, and $\alpha=\beta=90^\circ$ and $\gamma=120^\circ$ OR a=b=99±35, c=117±35, and $\alpha=\beta=90^\circ$ and $\gamma=120^\circ$. These methods are essentially the same with differences in beta secretase protein concentration during

crystallization. These working examples fail to provide the necessary guidance for making the entire scope of methods for crystallizing human beta secretase and crystals of beta secretase from any source including beta secretase having substitution of methionine with selenomethionine. The specification fails to provide guidance regarding alterations in the method of crystallization including the beta secretase protein and/or inhibitor or crystallization conditions, e.g., protein concentration, buffer components, concentrations, and pH, and temperature with an expectation of obtaining a crystal of human beta secretase or a crystal of *any* beta secretase with the space group symmetry or unit cell dimensions as recited in claims 72 and 73.

- The high degree of unpredictability in the art is supported by the state of the art: Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that protein crystallization is usually quite difficult to achieve and the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. teach that even small changes in the crystallization parameters, e.g., pH, can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). This is evidenced by the teachings of Chopra et al. (US 2002/0055459) and Tang et al. (US Patent 6,545,127). Chopra et al. teach crystallization of full-length human beta secretase complexed with a peptide inhibitor (shown at paragraph 0047 of Chopra et al.) in a buffer having 300 mM lithium sulfate, 25% PEG 8000, and 0.1 M sodium cacodylate, pH 6.5 with a resulting crystal having an orthorhombic space group symmetry of I222 (paragraph 0047). Also, Tang et al. (US Patent 6,545,127) teach crystallization of human beta secretase complexed with the inhibitor OM99-2 (shown in Figure 3B of Tang et al.) in a buffer having 30% PEG 8000, and 0.1 M sodium cacodylate, pH 6.4 with a resulting crystal having a orthorhombic space group symmetry of $P2_12_12_1$ (column 31, top). Thus, even minor modifications to a crystallization method may result in crystals that are distinct in structure having different space group symmetry and unit cell dimensions. Furthermore,

Hong et al. (*Science* 290:150-153) teach crystallization of the protease domain of human beta secretase complexed with a peptide inhibitor (shown in Figure 1 of Hong et al.) in a buffer having 0.2M ammonium sulfate, 22.5% PEG 8000, and 0.1 M sodium cacodylate, pH 7.4 at 20 degrees Celsius with a resulting crystal having a monoclinic space group symmetry of $P2_1$ (page 153, right column, top). Each of the above disclosed crystals is distinct in structure (based on the disclosed space group symmetry and unit cell dimensions) from one another and from the human beta secretase crystal produced by the method set forth at pages 45-47 of the specification. Thus, a skilled artisan would recognize the high degree of unpredictability in altering the crystallization parameters of a given protein, even slightly, with an expectation of obtaining a protein crystal with a *specific* space group symmetry or unit cell dimensions. The degree of unpredictability is further compounded as the claims are so broad as to encompass a method of crystallizing human beta-secretases or crystals of beta secretases having amino acid sequences that are distinct from that of SEQ ID NO:1, e.g., homologs and splice variants or having substitution of methionine with selenomethionine in the amino acid sequence of SEQ ID NO:1. The prior art teaches that at least one homolog and several splice variants of beta secretase have been isolated (see for example, Farzan et al. *Proc Natl Acad Sci, USA* 97:9712-9717 and Ehehalt et al. *Biochem Biophys Res Commun* 293:30-37) with amino acid sequences that are distinct from the human beta secretase of SEQ ID NO:1. Furthermore, replacement of methionine with selenomethionine in a given protein alters the amino acid and chemical composition of the protein. Thus, when crystallized, such homologs, splice variants, and selenomethionine mutants may pack differently forming different crystals from that of the protein of SEQ ID NO:1, even under identical crystallization conditions. The specification fails to provide sufficient guidance and/or working examples to predictably crystallize any beta secretase or human beta secretase under the given condition or with the resulting space group symmetry or unit cell dimensions. Also, it is well known in the art that a trigonal space group requires a=b in the unit cell dimensions and, as written, the unit cell dimensions of a and b as recited in claims 73 and 74 are not required to be equivalent. Furthermore, it is also well known in the art that a hexagonal crystal system has the unit cell dimensions of $\alpha=\beta=90^{\circ}$ and $\gamma=120^{\circ}$. As such, the unit cell dimensions of a, b, and c of claims 73 and 74

encompass a broad range of crystal lattices and/or unit cell dimensions and there is a high level of unpredictability in obtaining a crystal having a trigonal space group wherein a≠b or obtaining a hexagonal crystal of human beta secretase based on the teachings of the specification.

- The amount of experimentation required is undue: While methods of protein crystallization are known, it is *not* routine in the art to screen for all conditions for crystallizing a human beta secretase protein or to crystallize any beta secretase as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting Rejection(s)

[23] A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

[24] Claims 54-76 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-23 of copending Application No. 10/027,277 (hereafter referred to as "Application '277").

Claims 54-76 are identical in scope to claims 1-23 of Application '277. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

[25] Claims 54, 56, and 72-76 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 4, 5, and 24-28 of copending Application No. 10/144,441 (hereafter referred to as "Application '441"). Claims 54, 56, and 72-76 are identical in scope to claims 4, 5, and 24-28 of Application '441. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

[26] The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

[27] Claims 54, 55, and 57-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 6-23 of copending Application No. 10/144,441 (hereafter referred to as "Application '441"). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 54, 55, and 57-71 of the instant application and claims 1-3 and 6-23 of Application '441 are both directed to methods for crystallizing a human beta secretase in the presence of an inhibitor. The claims differ in that the pH of the solution of claim 54 is about 3.5 to about 5.5 whereas the pH of the solution of claim 1 of Application '441 is at most

about 6.0. The specification of Application '441 supports an embodiment that would anticipate claim 54 herein, i.e., a pH range of about 3.5 to about 5.5 (see for example claim 4 of Application '441). Claims 54, 55, and 57-71 cannot be considered to be patentably distinct over claims 1-3 and 6-23 of Application '441 when there is a specifically recited embodiment in Application '441 that would anticipate claims 54, 55, and 57-71 of the instant application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

[28] It is noted that at the time of drafting of the instant Office action, co-pending applications 10/143,723 and 10/435,533 were not available to the examiner. Once these applications become available, the claims will be evaluated for double patenting.

Conclusion

[29] Status of the claims:

- Claims 1-78 are pending
- Claims 1-53, 77, and 78 are withdrawn from consideration.
- Claims 54-76 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman
Patent Examiner
Art Unit 1652

08/09/03